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10/700,380	11/03/2003	Eveline Catherina Anna Clasina Timmermans	2183-5581.1US	9902

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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/700,380	CLASINA TIMMERMANS ET AL.	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *34-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 November 2003* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/3/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on February 28, 2006 is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112 - 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 13, 16, 19, 27, and 29 are indefinite because there is no nexus between the preamble and the claim steps. Claims 13, 16, 19, 27, and 29, in their respective preambles, are drawn to methods that accomplish a particular goal. However, none of the active claim step(s) states that this goal is accomplished. For clarity, claimed methods should recite that the purpose of the method has been attained (i.e. provide a nexus between the preamble and the claim steps).

(b) Claim 18 recites the limitation "the first cellular organelle nucleic acid" in line 2. There is insufficient antecedent basis for this limitation in the claim.

(c) Claims 28 and 30 are indefinite because it is unclear what is meant by the phrase --essentially related-- with regard to the comparison of organisms.

Claim Rejections - 35 USC § 112 - 1st Paragraph

With regard to the following rejections, it is noted that an enablement rejection art rejection are not contradictory, considering the fact that that the claimed methods are so broad as to encompass 1) Determining functioning of a cellular organism comprising the use of endosymbiotic organelle nucleic acid from *all* cellular organisms and 2) Determining various disease states of all diseases.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 13-18 and 27-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods employing relative ratios of mitochondrial nucleic acids to chromosomal nucleic acids, does not reasonably provide enablement for all types of relative ratios of nucleic acids from all organisms (e.g. ratios of chloroplast nucleic acids to chromosomal nucleic acids).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 13-18 and 27-33 are broadly drawn to methods for determining functioning of a cellular organism, toxic activity of a candidate compound for causing malfunction of cellular organism, and selective activity of a candidate compound against

a first organism. However, as will be further discussed, there is no support in the specification and prior art for the methods employing all types of relative ratios of nucleic acids from all endosymbiotic organelles from all organisms (e.g., ratios of chloroplast nucleic acids to chromosomal nucleic acids). The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification provides no evidence that the above methods were used to accomplish any of the claimed functions by employing, for example, relative ratios of nucleic acids from chloroplasts. Applicants did not show a single example pertaining to determination of functioning of a cellular organism, toxic activity of a candidate compound for causing malfunction of cellular organism, or selective activity of a candidate compound against a first organism by employing relative ratios of nucleic acids from chloroplasts. Therefore, with respect to this claimed subject matter, the specification provides no guidance whatsoever. With respect to methods employing relative ratios of mitochondrial DNA to chromosomal DNA, Applicants provided examples measuring relative amounts of mitochondrial DNA in cells from HIV-1 infected subjects undergoing treatment with anti-viral cocktails (Examples 2, 5, for example). However, no evidence or guidance is given as to how these specific examples correlate to relative ratios involving nucleic acids from endosymbiotic organelles specific to for

example plants (e.g. chloroplasts). Therefore, Applicants did not show any data pertinent to all other relative ratios currently encompassed by the claimed methods. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Working Examples

The specification has no working examples of evaluating to relative ratios involving nucleic acids from endosymbiotic organelles specific to plants (e.g. chloroplasts). Further, the only working examples are of HIV-1 infected subjects undergoing treatment with anti-viral cocktails with no guidance as to how these specific examples correlate to relative ratios involving nucleic acids from endosymbiotic organelles specific to plants (e.g. chloroplasts). No examples of the claimed methods were provided for any organisms other than humans, or any other endosymbiotic organelles other than mitochondria.

The unpredictability of the art and the state of the prior art

The determination of the amount of plastid DNA contained in mature eukaryotes has been the subject of recent studies, the conclusion of the studies being that there is evidence of "functioning" organisms that contain chloroplasts possessing no detectable DNA.

Rowan et al. ("The demise of chloroplast DNA in *Arabidopsis*, *Curr. Genet.* **46** (2004), pp. 176–181) recently published a study in which they stated that, "We conclude that there is a drastic reduction in the molecular size of chloroplast DNA structures during chloroplast development in *Arabidopsis* leaves. In many chloroplasts, the DNA

falls to undetectable levels well before the onset of senescence (Page 180, Column 1, Paragraph 3). Although DNA surely is essential during the early stages of leaf development, it is evident from our results that chloroplast genes are no longer required during the later stages of leaf development in *Arabidopsis*...(Page 180, Column 1, Discussion). In many chloroplasts, the DNA falls to undetectable levels well before the onset of senescence (Page 180, Column 1, Paragraph 3). Thus, the DNA in mature *Arabidopsis* chloroplasts might no longer be needed to support photosynthesis *Arabidopsis* (Page 181, Column 1, Paragraph 4)."

Similarly, Oldenburg et al. ("Changes in the structure of DNA molecules and the amount of DNA per plastid during chloroplast development in maize" J Mol Biol. 2004 Dec 10;344(5):1311-30") recently published a study in which they concluded that, "As we show here with maize,.., mature chloroplasts with no detectable DNA can persist in green leaves. DNA could be dispensable in mature chloroplasts if either photosynthetic proteins or mRNAs were stable (Page 1326, Column 2, Paragraph 1). The degradation of chloroplast DNA is not likely to trigger leaf senescence in maize because we find that adult leaves with chloroplast DNA persist for three months before showing any sign of yellowing (Page 1326, Column 1, Paragraph 1). We suggest that the degradation of chloroplast DNA during maize chloroplast maturation can benefit the plant in two ways. Nucleotides may be recycled for their nutritive value, and the elimination of chloroplast DNA relieves the cell of the burden of maintaining and repairing the many copies of the chloroplast genome that are no longer needed for their coding function (Page 1326, Column 1, Paragraph 2).

Therefore, these studies concluded that some mature eukaryotic organisms could contain chloroplasts possessing no detectable DNA. They further conclude that the lack of chloroplast DNA did not appear to have a significant association with leaf senescence. These results suggest that relative ratios involving nucleic acids from endosymbiotic organelles specific to plants (e.g. chloroplasts) are an unreliable predictor of for example, the "functioning" of some eukaryotic organisms.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply these methods using endosymbiotic organelles specific to plants (e.g. chloroplasts) for diagnostic purposes including the investigation of chloroplast genetics of a large number of organisms within several different environmental conditions to determine if "functional" defects are a result of chloroplast DNA depletion or another genetic variable. Further, effect of each of plant treatments (e.g. pesticides) alone and in all possible combinations with all other treatments given to organisms would have to be determined over long periods of time for statistically-significant groups of organisms, to determine if there exists a significant correlation between the chloroplast DNA levels in for example leaf cells and pesticide treatment. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the "functionality" of organisms possessing endosymbiotic organelles specific to plants (e.g. chloroplasts) do not seem to be correlated with chloroplast DNA depletion, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the relative ratios of nucleic acids from chloroplasts as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

2. Claims 16-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods relating to HIV-related diseases, does not reasonably provide enablement for methods relating to all diseases (e.g. tumor-related or angiogenic processes).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The nature of the invention and breadth of claims

Claims 16-26 are broadly drawn to methods for determining the staging of a disease and therapeutic activity and/or possible side-effects of a compound. However, as will be further discussed, there is no support in the specification and prior art for the methods relating to all diseases (e.g. tumor-related or angiogenic processes). The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification provides no evidence that the above methods were used to accomplish any of the claimed functions in subjects having or thought to have a tumor-related disease. Applicants did not show a single example pertaining to the determination of the staging of a disease or therapeutic activity and/or possible side-effects of a compound in subjects having or thought to have a tumor-related disease. Therefore, with respect to this claimed subject matter, the specification provides no guidance whatsoever. With respect to methods relating to subjects having HIV-1

related diseases, Applicants provided examples measuring relative amounts of mitochondrial DNA in cells from HIV-1 infected subjects undergoing treatment with anti-viral cocktails (Examples 2, 5, for example). However, no evidence or guidance is given as to how these specific examples correlate to subjects having or thought to have a tumor-related disease. Therefore, Applicants did not show any data pertinent to all other diseases (e.g. tumor-related or angiogenic processes) currently encompassed by the claimed methods. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Working Examples

The specification has no working examples of evaluating to relative ratios involving nucleic acids from subjects having or thought to have a tumor-related disease. Further, the only working examples are of HIV-1 infected subjects undergoing treatment with anti-viral cocktails with no guidance as to how these specific examples correlate to subjects having or thought to have a tumor-related disease.

The unpredictability of the art and the state of the prior art

The determination of the amount of mitochondrial DNA contained in tumor cells has been the subject of several studies, the general conclusion of the studies being that the amount of mitochondrial DNA contained within the tumor tissue is extremely unpredictable between different types of cancer.

Penta et al recently published an article entitled "Mitochondrial DNA in human malignancy" (Mutation Research/Reviews in Mutation Research, Volume 488, Issue 2, May 2001, Pages 119-133) in which they conclude that:

"Tumor cells, in general, have increased levels of mtDNA transcripts (mRNA), while both increases and decreases in the levels of tumor cell mtDNA have been reported. Experiments from Wallace and colleagues [107] involving three pairs of human diploid fibroblasts and their SV-40-transformed counterparts revealed that the mRNA levels for a variety of mtDNA-encoded genes were increased, while the level of mtDNA decreased. Similarly, an increase in the level of mtDNA transcripts has been reported for viral and cellular oncogene-transformed rat fibroblasts [123], chemically induced hepatomas [124], and in familial polyposis coli intestinal polyps [45], with no alteration of mtDNA levels. On the other hand, primary low-grade human brain tumors (gliomas) showed an increased copy number for regions of the mitochondrial genome, which was accompanied by increased nuclear localization of these regions [125]. Amplification of mtDNA has also been reported in acute myeloid leukemia [126]. Paradoxically, many tumor cells show a decrease in mitochondrial mass of approximately 50% [59]. However, the precise relationship between mitochondrial mass, the level of mitochondrial mRNA, and mtDNA copy number has yet to be examined. Since rat fetal liver has about one-half the mitochondrial mass of adult liver, it has been proposed that there is an association between rapid growth and reduced mitochondrial mass.

Thus, as highlighted by Penta, the general state of the prior art suggests that the amount of mitochondrial DNA contained within the tumor tissue is entirely unpredictable between different types of cancer. These results suggest that relative ratios involving nucleic acids from mitochondria specific to plants tumor tissue are an unreliable predictor of for example, the "staging" of cancer.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply these methods for diagnostic purposes including the investigation of mitochondrial genetics of a large number of tumor-negative and tumor-positive patients to determine the particular stage of the disease, i.e., for example, whether an increase or decrease in mitochondrial DNA is an indicator of tumor tissue formation. Further, effect of each of the drugs alone and in all possible combinations with all other drugs given to tumor-positive patients would have to be determined over long periods of time for statistically-significant groups of patients, to determine if there exists a significant correlation between the mitochondrial DNA levels in tumor cells or each of the drugs alone and for certain drug combinations. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the "staging" of a tumor-related disease does not seem to be correlated with a mitochondrial DNA increase or depletion, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the relative ratios of nucleic acids from chloroplasts as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1-3, 8-11, 13, 16, 19, 27, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Tabiti et al. (EP 1 138 783 A2).

With regard to Claim 1, Tabiti et al. teach a method (Pages 11-13, for example) comprising: amplifying the nucleic acids of interest in the amplification reaction (Page 11, Example 1, for example); measuring the amount of at least two nucleic acids of interest at at least two different time points in the reaction (Page 11, Example 1, for example); determining from at least two of the measurements the amplification rate of the at least two nucleic acids of interest (Pages 11,12, Example 2, for example); comparing the rates with a reference (Page 12, Example 3, for example); and determining, from the comparison, the initial ratio of the amounts of the at least two nucleic acids of interest in the sample (Page 12, Example 3, for example);. Tabiti further teaches multiplex amplification/detection (Page 8, [0044], for example).

With regard to Claims 2, 3, and 8, Tabiti expressly teaches variable salt concentration that allow detectable levels of all nucleic acids of interest (Page 13, Example 4, for example).

With regard to Claim 9, Tabiti expressly teaches independent nucleic acids of interest (Page 11, Example 1, for example).

With regard to Claims 10 and 11, Tabiti expressly teaches RNA (Page 11, Example 1, for example) and DNA (Page 13, Example 4, for example) nucleic acids of interest.

With regard to Claims 13, 16, 19, 27, 29, as noted above, phrases such as -- for determining functioning of a cellular organism -- contained in the preamble is considered an *intended use* of the active method steps and does not incorporate a patentably distinct feature. Furthermore, as noted above, there is no nexus between the preamble and the claim steps. Thus, the instant claims are anticipated by the teachings of Tabiti (Pages 11-13, for example); please refer to the rejection of Claim 1 above.

1. Claims 1-11, 13-22, 24, and 27-34 are rejected under 35 U.S.C. 102(e) as being anticipated by Stuyver et al. (U.S. 2003/0124512 A1).

With regard to Claim 1, Stuyver et al. teach a method (Pages 8-10, for example) comprising: amplifying the nucleic acids of interest in a multiplex amplification reaction; measuring the amount of at least two nucleic acids of interest at at least two different time points in the reaction; determining from at least two of the measurements the amplification rate of the at least two nucleic acids of interest; comparing the rates with a reference; and determining, from the comparison, the initial ratio of the amounts of the at least two nucleic acids of interest in the sample (Pages 22,23, Example 11, for example).

With regard to Claims 2-8, Stuyver expressly teaches optimization of real-time RT-PCR including varying primer concentrations and salt concentrations (Pages 19,20, Example 5, for example).

With regard to Claim 9, Stuyver expressly teaches independent nucleic acids of interest (Pages 22,23, Example 11, for example).

With regard to Claims 10 and 11, Stuyver expressly teaches RNA and DNA nucleic acids of interest (Pages 22,23, Example 11, [0311], for example).

With regard to Claims 13, 16, 19, 27, 29, as noted above, phrases such as -- for determining functioning of a cellular organism-- contained in the preamble is considered an *intended use* of the active method steps and does not incorporate a patentably distinct feature. Furthermore, as noted above, there is no nexus between the preamble and the claim steps. Thus, the instant claims are anticipated by the teachings of Stuyver (Pages 11-13, for example); please refer to the rejection of Claim 1 above.

With regard to Claim 14, Stuyver expressly teaches endosymbiont cellular organelle nucleic acid (Page 13, [0190], for example).

With regard to Claim 15, Stuyver expressly teaches determining the ratio of the amount of endosymbiont cellular organelle nucleic acid in relation to the amount of nuclear nucleic acid (Pages 22,23, Example 11, for example).

With regard to Claim 17, Stuyver expressly teaches HIV (Page 13, [0196]-[0197], for example).

With regard to Claim 18, Stuyver expressly teaches RNA and DNA nucleic acids of interest (Pages 22,23, Example 11, [0311], for example).

With regard to Claim 20, Stuyver expressly teaches HIV (Page 13, [0196]-[0197], for example).

With regard to Claims 21, 22, and 24, Stuyver expressly teaches nucleotide analogues and AZT (Page 25, Example 14, for example).

With regard to Claims 28, 30, and 31, Stuyver expressly teaches toxicity assays (Page 25, Example 14, for example).

With regard to Claims 32 and 33, Stuyver expressly teaches determining the ratio of the amount of endosymbiont cellular organelle nucleic acid in relation to the amount of nuclear nucleic acid (Pages 22,23, Example 11, for example).

With regard to Claim 34, Stuyver expressly teaches peripheral blood mononuclear cells (Page 22, [0301], for example).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tabiti et al. (EP 1 138 783 A2) in view of Henegariu et al. ("Multiplex PCR: Critical Parameters and Step-by-step Protocol" BioTechniques. September 1997. 23: Pages 504-511).

With regard to Claims 4-7, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach varying primer concentration.

Henegariu et al. teaches optimization of multiplex reaction components such as primer concentration or primers directed to different loci (Page 508, Figure 3c, for example). They further teach overcoming uneven amplification by changing the proportions of various primers in the reactions, with an increase in the amount of primers for the "weak" loci and a decrease in the amount for the "strong" loci (Page 508, Column 1, Amount of primer, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate to optimize the primer concentrations of the multiplex reaction of Tabiti since Henegariu suggests such a modification to correct for uneven amplification.

2. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tabiti et al. (EP 1 138 783 A2) in view of van Deursen et al. ("A novel quantitative multiplex NASBA method: application to measuring tissue factor and CD14 mRNA levels in human monocytes" Nucleic Acids Res. 1999 Sep 1;27(17):e15).

With regard to Claim 12, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach multiplex quantitative nucleic acid sequence based amplification (NASBA).

van Deursen et al. teaches quantification of RNA levels in a multiplex setting (Page ii, NASBA, for example). They further teach that since the NASBA reaction is isothermal, specific amplification of single-stranded RNA in the presence of double-stranded DNA is possible (Page 508, Column 1, Amount of primer, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate to quantitative multiplex NABSA reaction of van Deursen into the methods of Tabiti since van Deursen suggests such a modification to correct for amplification of single-stranded RNA in the presence of double-stranded DNA.

3. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stuyver et al. (U.S. 2003/0124512 A1) in view of van Deursen et al. ("A novel quantitative multiplex NASBA method: application to measuring tissue factor and CD14 mRNA levels in human monocytes" Nucleic Acids Res. 1999 Sep 1;27(17):e15).

With regard to Claim 12, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach multiplex quantitative nucleic acid sequence based amplification (NASBA).

van Deursen et al. teaches quantification of RNA levels in a multiplex setting (Page ii, NASBA, for example). They further teach that since the NASBA reaction is isothermal, specific amplification of single-stranded RNA in the presence of double-stranded DNA is possible (Page 508, Column 1, Amount of primer, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate to quantitative multiplex NABSA reaction of van Deursen into the methods of Stuyver since van Deursen suggests such a modification to correct for amplification of single-stranded RNA in the presence of double-stranded DNA.

3. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stuyver et al. (U.S. 2003/0124512 A1) in view of Krynetskaia et al. ("Deoxythioguanosine triphosphate impairs HIV replication: a new mechanism for an old drug" FASEB J. 2001 Sep;15(11):1902-8).

With regard to Claim 23, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not

expressly teach determining the therapeutic activity of the compounds set forth in Claim 23.

Krynetskaia et al. teaches an assay determining the anti-HIV activity of thioguanine (Page 1904, Column 1, for example). They further teach that thiopurines represent a new class of agents with anti-retroviral activity (Page 1907, Column 2, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate to thioguanine into the methods of Stuyver since Krynetskaia suggests such a modification to test its anti-retroviral activity.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

It is noted that only representative claims will be discussed.

1. Claims 1 and 13-34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claim 11 of van Gemen et al. (U.S. 6,967,016 B2).

With regard to Claim 1, as noted above, the phrase --for determining functioning of a cellular organism-- contained in the preamble is considered an *intended use* of the active method steps and does not incorporate a patentably distinct feature. Similarly, the phrase -- of determining whether a medicament has therapeutic activity and/or possible side-effects-- contained in the preamble as in Claim 11 of van Gemen et al. ('016) is considered an *intended use* of the active method steps and does not incorporate a patentably distinct feature.

Claim 11 of van Gemen et al. ('016) recites a method comprising: introducing a medicament to an organism; determining in a sample obtained from said organism a relative ratio of a mitochondrial nucleic acid and/or gene product thereof to a chromosomal nucleic acid and/or gene product thereof; and determining whether there is a change in the relative ratio during and/or after introduction of the medicament, wherein said change in said relative ratio is indicative that said medicament has therapeutic activity and/or possible side-effects; wherein said relative ratio of said mitochondrial nucleic acid and/or gene product thereof to said chromosomal nucleic acid and/or gene product thereof is determined in a single assay; further comprising

amplifying said mitochondrial nucleic acid and/or gene product thereof and said chromosomal nucleic acid and/or gene product thereof in a single assay.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to the same general inventive concept of determining the initial ratio of the amounts of at least two nucleic acids of interest in a sample in a multiplex setting. The method set forth in Claim 11 of van Gemen et al. ('016) represents a species of the genus method set forth in Claim 1 of the instant application. The recitation of a species renders the genus obvious.

2. Claims 2-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claim 11 of van Gemen et al. (U.S. 6,967,016 B2) in view of Henegariu et al. ("Multiplex PCR: Critical Parameters and Step-by-step Protocol" BioTechniques. September 1997. 23: Pages 504-511).

With regard to Claims 2-8, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach varying primer concentration.

Henegariu et al. teaches optimization of multiplex reaction components such as primer concentration of primers directed to different loci (Page 508, Figure 3c, for example) and salt concentration (Page 508, Figure 4c, for example). They further teach overcoming uneven amplification by changing the proportions of various primers in the reactions, with an increase in the amount of primers for the "weak" loci and a decrease

in the amount for the "strong" loci (Page 508, Column 1, Amount of primer, for example). They further teach increased specificity of multiplex amplification through salt optimization (Page 408, Column 3, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate to optimize the primer concentrations of the multiplex reaction of van Gemen since Henegariu suggests such a modification to correct for uneven amplification.

3. Claim 12 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claim 11 of van Gemen et al. (U.S. 6,967,016 B2) in view of van Deursen et al. ("A novel quantitative multiplex NASBA method: application to measuring tissue factor and CD14 mRNA levels in human monocytes" Nucleic Acids Res. 1999 Sep 1;27(17):e15).

With regard to Claim 12, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach multiplex quantitative nucleic acid sequence based amplification (NASBA).

van Deursen et al. teaches quantification of RNA levels in a multiplex setting (Page ii, NASBA, for example). They further teach that since the NASBA reaction is isothermal, specific amplification of single-stranded RNA in the presence of double-stranded DNA is possible (Page 508, Column 1, Amount of primer, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate to quantitative multiplex NABSA reaction of van Deursen into the methods of van Gemen since van Deursen suggests such a modification to correct for amplification of single-stranded RNA in the presence of double-stranded DNA.

Conclusion

Claims 1-34 are rejected. No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Cote et al. (U.S. 2003/0099933 A1).

Sanger et al. (U.S. 6,691,041 B1).

Meijernink et al. ("A novel method to compensate for different amplification efficiencies between patient DNA samples in quantitative real-time PCR" J Mol Diagn. 2001 May;3(2):55-61.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

5/30/06

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